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Synthesis of benzopyranopyrrolidines via 1,3-dipolar cycloaddition of nonstabilized azomethine ylides with 3-substituted coumarins

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ABSTRACT

A three-component reaction of 3-substituted coumarins with *N*-alkyl-α-amino acids and aldehydes gave 1-benzopyrano[3,4-*c*]pyrrolidines as a result of a 1,3-dipolar cycloaddition of an intermediate non-stabilized azomethine ylide at the double bond of the coumarin system in moderate to good yields. In most cases, high regio- and stereo-selectivity of the [3+2] cycloaddition was observed.

1. Introduction

A decarboxylative reaction of *N*-alkyl-α-amino acids with carbonyl compounds is one of the most convenient methods to generate nonstabilized azomethine ylides for [3+2] cycloaddition with electron-deficient alkenes.[1] As this method has been developed relatively recently, by Grigg and Tsuge in the late 1980s, the chemistry of nonstabilized azomethine ylides obtained in these reactions is studied significantly less in comparison with other 1,3-dipoles.[2] Their reactions with 3-substituted coumarins are interesting, first, to study the regio- and stereo-selectivity of the cycloaddition with asymmetric trisubstituted alkenes; second, in view of the biological activity of adducts.

It has been found that *R*,*R*-benzopyranopyrrolidine **1** is an α_1 adrenoreceptor antagonist, whereas *R*,*R*-benzopyranopyrrolidine **2** is an antagonist of 5-HT_{2C} receptors with respect to 5-HT_{2A}.[3] Benzopyranopyrrolidine **1** named Fiduxosin shows an α_{1a}/α_{1b} selectivity for adrenoreceptors; it was suggested as a promising pharmaceutical agent for the treatment of benign prostatic hyperplasia.[3f] Very recently, the synthesis of isomeric 2-benzopyranopyrrolidine **3**, which was found to be serotonin 5-HT_{2C} receptor agonist has been reported[3g] (Fig. 1).

The key stage in the synthesis of compounds **1** and **2** consists of a cycloaddition of nonstabilized azomethine ylides onto benzopyranones; however, information about such reactions in the coumarin series was quite limited.[2e,f,3g] In a preliminary communication,[4] we described the synthesis of 1-benzopyrano[3,4-*c*]pyrrolidines from 3-substituted coumarins and a symmetric azomethine ylide derived from sarcosine and formaldehyde. [3+2] cycloaddition of these coumarins with asymmetric ylides generated from proline and

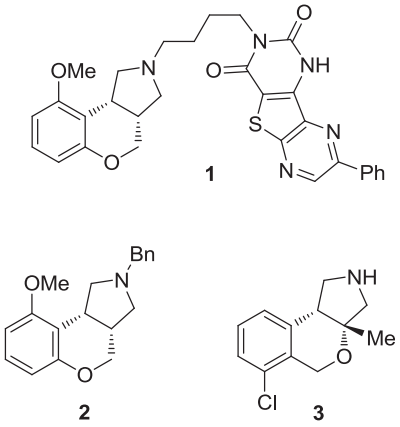

Fig. 1. Benzopyranopyrrolidine drugs candidates.

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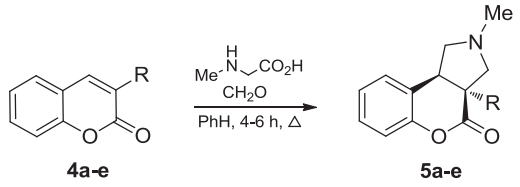
formaldehyde or benzaldehyde gave one diastereomer after crystallization of salts and indicated a good selectivity of the reaction. Given the broad utility of benzopyranopyrrolidines in medicinal chemistry and continuing our research in this field,[5,6] we have extended this to a number of coumarins and azomethine ylides, as well as isolating some minor diastereomers and establishing their structures. In addition, the study of the chemical properties of the adducts has begun.

2. Results and discussion

2.1. 1,3-Dipolar cycloaddition of nonstabilized azomethine ylides with 3-substituted coumarins

We have found that refluxing of sarcosine, paraformaldehyde and coumarins **4a**–**e** in benzene for 4–6 h with azeotropic removal of water results in benzopyranopyrrolidine derivatives **5a**–**e** (yields 76–92%) (Scheme 1). Treatment of products **5a**,**c** with oxalic acid provided conversion of these liquid pyrrolidines into analytically pure crystalline oxalates without chromatographic purification. Adducts **5b**,**d**,**e** were purified by flash chromatography using silica gel. On the other hand, 3-methylcoumarin reacts very sluggishly with this ylide, and after refluxing for 7 h only 27% of the desired product was observed in the crude reaction mixture according to the ^{1}H NMR spectroscopic data.



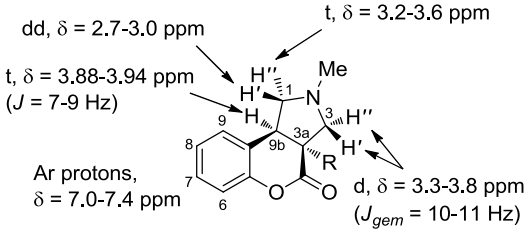
4a-e **5a-e**

Comp. **4**, **5**	R	Yield (%)	Product's form	Mp (°C)
a	H	78	oxalate	191–193
b	CN	76	free base	liq.
c	CO_2Et	84	oxalate	164–166
d	$CONMe_2$	87	free base	96–98
e	$PO(OEt)_2$	92	free base	126–128

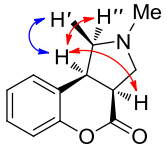
Scheme 1. Synthesis of 2-methyl-4-oxo-1,2,3,3a,4,9b-hexahydrochromeno[3,4-*c*]pyrroles **5a**–**e**.

The structures of products **5a**–**e** were determined by elemental analyses, HRMS and their ^{1}H and ^{13}C NMR spectra as well as 2D ^{1}H–^{13}C HMQC, HMBC, and ^{1}H–^{1}H NOESY experiments. The ^{1}H NMR spectra of oxalates **5a**,**c**,**d** in DMSO-d_6 contain the characteristic signals: a doublet of doublets for the H-1′ proton at δ 2.7–3.0 ppm, which is subject to the shielding effect of the benzene moiety in the *cis*-position; a triplet for H-1″ at δ 3.2–3.6 ppm (this proton manifests itself at δ 3.20–3.27 ppm in the presence of an ethoxycarbonyl or dimethylamide group at the 1,3-*cis*-position that show a shielding effect[7]); two doublet of doublets or two doublets for the H-3′ and H-3″ geminal protons at δ 3.3–3.8 ppm (J_{gem}=10–11 Hz); a quartet or a triplet for the H-9b benzyl proton at δ 3.88–3.94 ppm (J=7–9 Hz). The signals for the H-6 and H-8 aromatic protons are observed at δ 7.03–7.06 and 7.14–7.17 ppm, respectively, whereas the partially overlapping signals for H-7 and H-9 appeared at δ 7.25–7.35 ppm. It is well known that synchronism of the reactions of nonstabilized azomethine ylides with alkenes results in a *cis*-fusion in the new pyrrolidine ring.[1–3] This was confirmed in the ^{1}H–^{1}H NOESY experiment of the oxalate **5a** by considering the cross-peaks intensities of proton H-9b with H-1′, H-1″, and H-3a (Fig. 2).

*^{1}H NMR (400 MHz, DMSO-d_6) data of the oxalates **5a,c,d***



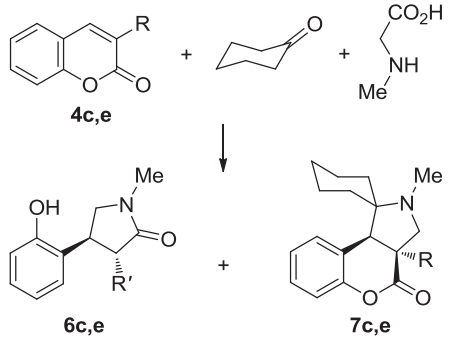
*^{1}H-^{1}H NOESY cross-peaks of the oxalate **5a***



red - strong NOE interactions
blue - weak NOE

Fig. 2. Diagnostic ^{1}H NMR signals and NOE correlations of benzopyranopyrrolidine oxalate **5a**.

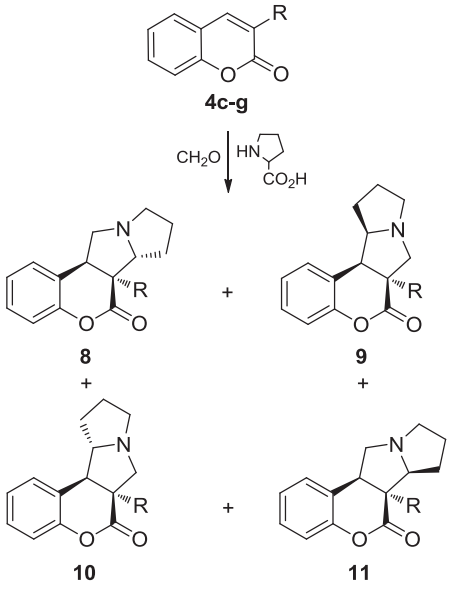
Reaction of 3-substituted coumarins with the asymmetrical nonstabilized azomethine ylide generated in situ by the condensation of sarcosine and cyclohexanone led to unexpected results (Scheme 2). This ylide reacted with coumarins **4c**,**e** to give 4-aryl-2-pyrrolidones **6c**,**e** as the major products in 30% and 47% yields, respectively. A possible mechanism for their formation has been described previously.[5] For this reason, the yields of adducts **7c**,**e** resulting from the classical 1,3-dipolar cycloaddition were considerably reduced (17% and 20%, respectively). Compounds **7c**,**e** were isolated from a crude reaction mixture by simple acidification with dilute HCl (5 equiv) followed by separation of the aqueous layer, neutralization with $NaHCO_3$, and subsequent flash chromatography over silica gel (Scheme 2).



R = CO_2Et (**c**), $PO(OEt)_2$ (**e**)
R′ = $CONMe_2$ (**c**), $PO(OEt)_2$ (**e**)

Scheme 2. Reaction with asymmetrical azomethine ylides from sarcosine and cyclohexanone.

We have also examined the cycloaddition behaviour of proline and formaldehyde using coumarins **4** as the trapping dipolarophiles and found that fused pyrrolizidines **8** are produced as the major products (Scheme 3). The reactions of coumarins **4a**,**b** with proline and formaldehyde resulted in the formation of complex and difficult to separate mixtures of isomers and their hydrolysis products. In contrast, coumarins **4c**–**g** gave much more stable adducts. According to the ^{1}H NMR data, the crude reaction mixture of the cycloaddition with 3-ethoxycarbonylcoumarin (**4c**) consisted of four diastereomers with the stereochemistry as shown (Scheme 3).



Coumarin 4	R	Ratio in a crude mixture (%)[a] 8	9	10	11	Yield (%)[b]
c	CO_2Et	60	19	15	6	47
d	$CONMe_2$	did not measure				60
e	$PO(OEt)_2$	62	19	14	5	44
f	COPh	62	18	15	5	50
g	Me	0	6	3	91	41[c]

[a] The ratio was determined from ^1H and ^{31}P NMR data.
[b] Yield of **8**.
[c] Yield of **11**.

Scheme 3. Reaction of coumarins **4c**–**g** with proline and formaldehyde.

The major reaction product was **8c** (60%) but in addition, small amounts of **9c** (19%) as well as **10c** (15%) and **11c** (6%) could also be detected. Three of them, **8c**, **9c** and **10c**, were isolated by column chromatography and their structures were clearly established on the basis of 1D and 2D NMR spectroscopic data. Coumarin-3-phosphonate (**4e**) reacted with the ylide derived from proline and paraformaldehyde in a similar manner, and the major adduct **8e** and one minor diastereomer **9e** were isolated by column chromatography. Furthermore, compounds **8c**,**e** could also be obtained without the use of chromatography, by simple recrystallization of oxalates from ethanol. A similar cycloaddition was also found to occur when 3-dimethylcarbamoylcoumarin (**4d**) and 3-benzoylcoumarin (**4f**) were used. In this case, pyrrolizidines **8d**,**f** were obtained after recrystallization of the crude oxalates in good yields. In contrast to this, the reaction of 3-methylcoumarin (**4g**) under the same conditions led to the formation of the essentially one diastereomer **11g**, which was isolated as the hydrochloride in 41% yield. This compound was the main component of the reaction mixture (91% according to the ^1H NMR spectrum) (Scheme 3).

On the basis of compounds **8c**–**11c**, obtained from 3-ethoxycarbonylcoumarin (**4c**), one can see how the structures of all the products **8**–**11** were established (Fig. 3). The two pairs of regioisomers are easily distinguished according to the ^1H NMR data, because they have different proton multiplicity in the central pyrrolidine ring (in pair **9** and **10** there is an isolated methylene group). The stereochemistry of **8c**–**11c** was assigned by ^1H–^1H NOESY experiments. In the case of diastereomers **8c** and **11c**, there is a cross-peak for the deshielded H-11″ with H-9 (isomer **8c**) and

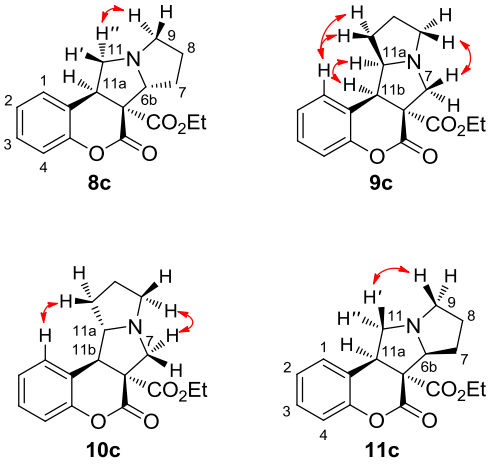
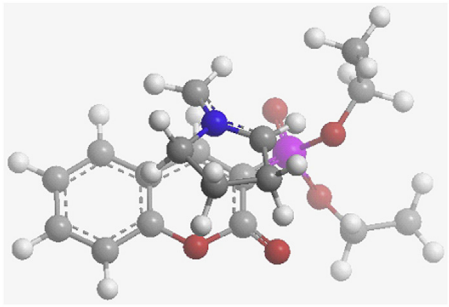


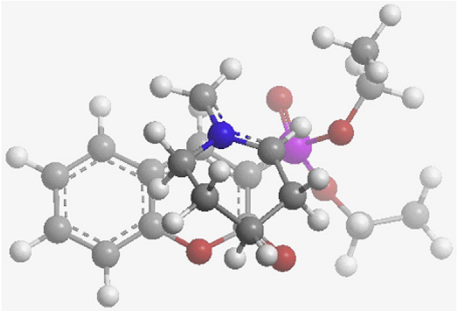
Fig. 3. ^1H–^1H NOESY data of pyrrolizidines **8c**–**11c**.

a cross-peak for shielded H-11′ with H-9 (isomer **11c**). Stereoisomers **9c** and **10c** differ in the chemical shifts of the methine proton H-11a. In the case of *trans*-fusion in the pyrrolizidine **10c**, this proton was observed at a 0.65 ppm higher magnetic field than that of **9c** with *cis*-fusion, probably due to a shielding effect of the benzene ring.[4,7] In addition, a strong NOE cross-peak was observed between H(11a)–H(11b) in isomer **9c**. The structures of products **8**–**11** were confirmed by elemental analyses, HRMS, ^{13}C NMR spectra as well as 2D ^1H–^{13}C HMQC and HMBC experiments.

In general, all coumarins with an electron-withdrawing group in the 3-position reacted with the azomethine ylide derived from proline and formaldehyde in a similar manner. A favourable transition state taking into account molecule polarity would lead to stereoisomers *exo*-**8** and *endo*-**11**. Apparently, the second *endo*-direction was almost completely suppressed by the unfavourable steric interactions of the hydrogens of the azomethine ylide and the pyrone core (Fig. 4). In the case of 3-methylcoumarin, the



endo-**TS 1** (for **11e**)

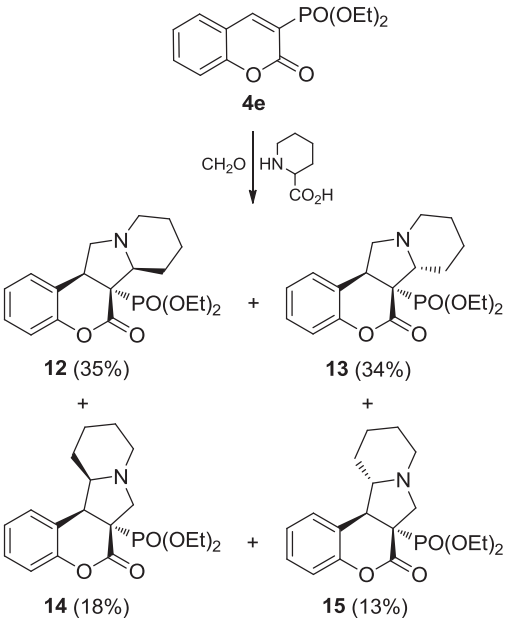


endo-**TS 2** (for **12**)

Fig. 4. Plausible transition states for compounds **11e** and **12**.

endo-diastereomer **11** was formed in a large excess relative to the other isomers. Probably, the crucial change in cycloaddition selectivity is associated with domination of steric interactions of the ylide with the coumarin methyl group.

To our knowledge, very little information is available on the generation of an azomethine ylide from pipecolic acid and formaldehyde. It has only been reported that 1,2-diaroylethenes react to give a mixture of the isomeric perhydroindolizines.[8] We found that the reaction of coumarin-3-phosphonate (**4e**) with pipecolic acid and paraformaldehyde gave a mixture of the corresponding four stereoisomers **12** (35%), **13** (34%), **14** (18%), and **15** (13%). These indolizidines have been separated by column chromatography but the main products **12** and **13** still were as a mixture (39% of **12** and 61% of **13**). As in the case of cycloaddition reactions involving proline, similar NOE cross-peaks revealed the stereochemistry of isomers **12**–**15** (Scheme 4).

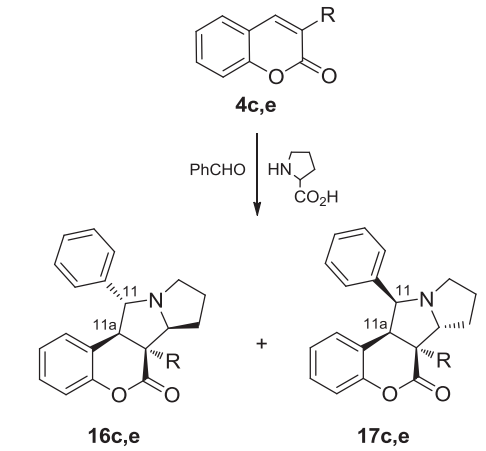


Scheme 4. Synthesis of indolizidines **12**–**15**.

The selectivity of this azomethine ylide interaction differs from the interaction of the ylide derived from proline and formaldehyde. Apparently such distinction is due to the size and flexibility of its cyclic moiety. The absence of adverse steric interactions between the hydrogen atoms of the bigger non-planar ylide with the coumarin pyran ring significantly increases *endo*-cycloaddition (Fig. 4).

In addition to paraformaldehyde and cyclohexanone, benzaldehyde was briefly examined in the reaction. Cycloaddition of 3-ethoxycarbonylcoumarin (**4c**) with the azomethine ylide derived from proline and benzaldehyde resulted in a mixture of a large number of pyrrolizidines. Two of them, **16c** and **17c**, are the major products and were isolated as a 36:64 mixture, respectively, by column chromatography in 37% yield. Alternative separation of the isomers, conversion to the hydrochlorides and crystallization from ethyl acetate–acetone mixture, allowed us to obtain pure diastereomer **17c** as the hydrochloride in 26% yield. Coumarin-3-phosphonate (**4e**) reacted in a similar way to give adducts **16e** and **17e** as free bases after column chromatography in 33% and 21% yields, respectively (Scheme 5).

The ^{1}H NMR spectra of the resulting products allowed us to establish their stereochemistry only partially. An alternative regioisomer can be ruled out from consideration because of the multiplicity of the benzylic proton H-11, which appeared as



Comp. **16**, **17**	R	Ratio in a crude mixture (%)[a]		Yield (%)	
		16	**17**	**16**	**17**
c	CO_2Et	39	32	37[b]	26[c]
e	$PO(OEt)_2$	55	28	33	21

[a] The ratio was determined from ^{1}H and ^{31}P NMR data.
[b] A mixture **16c** : **17c** = 36 : 64.
[c] Isolated as the hydrochloride.

Scheme 5. Reaction of coumarins **4c**,**e** with proline and benzaldehyde.

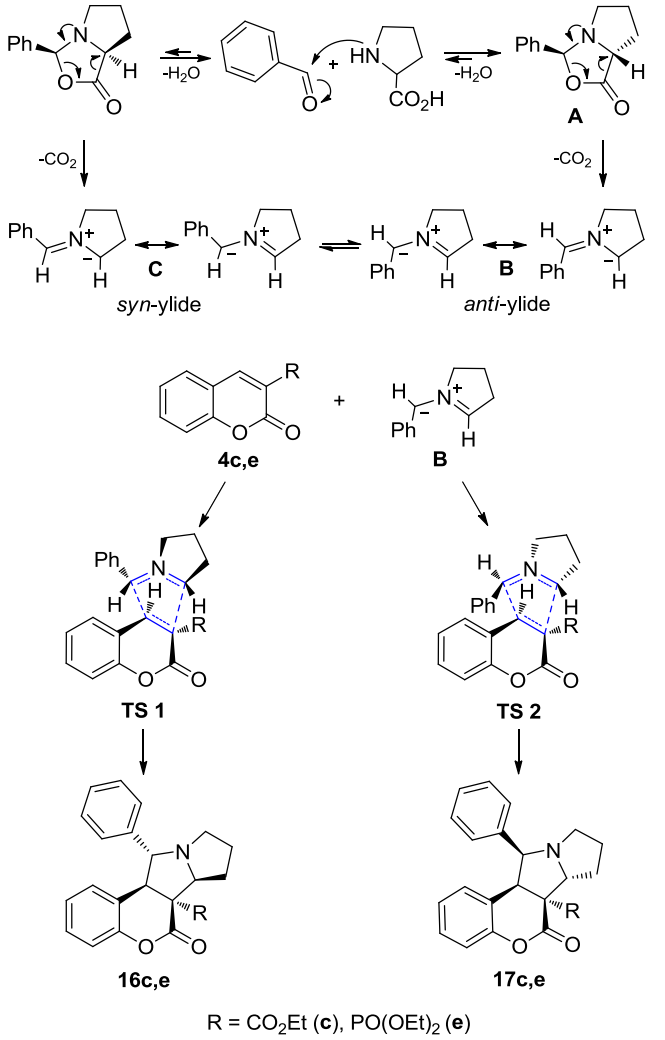
a doublet. Significantly shielded signals for benzylic protons H-11 and H-11a in diastereomers **16** allows us to assign the phenyl rings as *trans*-arranged. Strong evidence for the structures **16c**,**e** and **17c**,**e** was obtained from the ^{1}H–^{1}H NOESY experiments. The most informative cross-peaks for these compounds are as follows: H-11/H-11a (for **17**) and H-11/H-9 (for **16** and **17**). The structure of hydrochloride **17c** has been confirmed using X-ray diffraction data.[4]

This 1,3-dipolar cycloaddition occurs with *anti*-azomethine ylide **B** via two different transition states following from structures **16** and **17**. The formation of the ylide **B** can be explained by the higher stability of *trans*-azalactone **A** that is initially formed in the reaction of proline with benzaldehyde. Concerted cycloreversion of the azalactone ring in **A** with extrusion of carbon dioxide follows a disrotatory pathway to give *anti*-ylide **B**. Apparently, the isomerization of dipoles **B** and **C** have small rate constants, and the reaction of **B** with coumarins **4e**,**c** becomes the main direction (Scheme 6).[2e,f]

2.2. Representative reactions of compounds 5

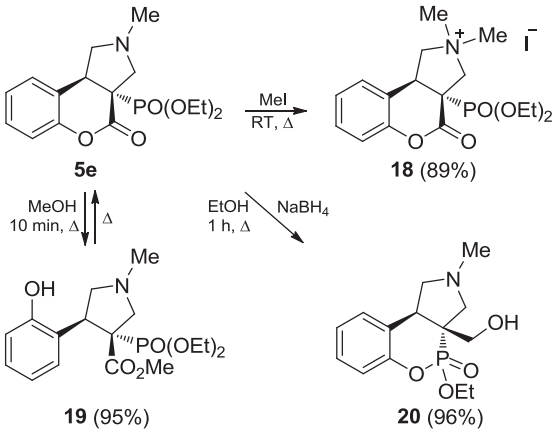
In the second part of this work, we studied some reactions of compounds **5** (Scheme 7). It was found that 1-benzopyrano[3,4-*c*] pyrrolidine **5e** readily undergoes quaternization with methyl iodide to give salt **18** in high yield. Briefly refluxing **5e** in methanol resulted in the opening of the dihydrocoumarin ring to form methyl ether **19**. It should be noted that heating of **19e** on a rotary evaporator greater than 70 °C promotes a reverse reaction. Reduction with sodium borohydride in ethanol led to corresponding alcohol with concomitant recyclization to produce compound **20**. The structures of products **18**–**20** were deduced from their satisfactory elemental and spectroscopic (^{1}H, ^{31}P NMR, and HRMS) studies (Scheme 7).

Oxalates **5b**,**d** were found to be highly hygroscopic compounds. Judging by the ^{1}H NMR spectra, they undergo partial hydrolysis in a DMSO-d_6 solution with opening of the dihydrocoumarin ring (a set of the aromatic phenolic protons was observed at δ 6.7–7.1 ppm).

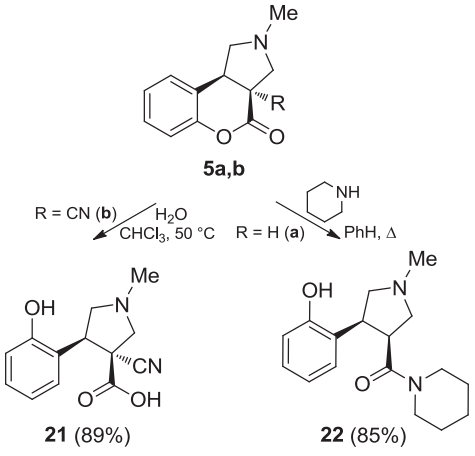


Scheme 6. A plausible reaction route to compounds **16** and **17**.

Even gentle heating (50 °C) of free base **5b** in wet chloroform resulted in opening of the dihydrocoumarin ring by water to form a corresponding amino acid **21** (Scheme 8). Clearly, it is due to the presence of a good leaving phenolate group, and the basic nitrogen atom. It should be noted that salts of pyrrolidines **5a**,**c** are more resistant to nucleophiles; oxalates can be purified by recrystallization from ethanol (prolonged heating in ethanol leads to their partial ring-opening). Benzopyranopyrrolidine **5a**



Scheme 7. Reactions of the adduct **5e**.



Scheme 8. A nucleophilic ring-opening of **5a**,**b**.

smoothly reacted with piperidine to produce amide **22** in 85% yield (Scheme 8).

3. Conclusion

The use of 3-substituted coumarins, *N*-alkyl-α-amino acids and aldehydes in [3+2] cycloadditions gives 1-benzopyrano[3,4-*c*]pyrrolidine derivatives with good regio- and stereo-selectivity, depending on the nature of a substituent in the pyranone ring. These products are interesting in view of their potential biological activity, as well as being building blocks in pharmaceutical chemistry. A general chemical property of these adducts to undergo nucleophilic ring-opening of the pyranone cycle was described.

4. Experimental

4.1. General

NMR spectra were obtained on a Jeol ECX-400 spectrometer operating at 400 MHz for ^{1}H (TMS), 162 MHz for ^{31}P (H_3PO_4) and 101 MHz for ^{13}C (TMS). All measurements were recorded in DMSO-d_6 or $CDCl_3$ solutions. IR spectra were recorded on a Thermo Scientific Nicolet 6700 Fourier IR spectrometer (ATIR). Mass spectrometry was established on a MicroTOF-Q fitted with an ESI source. Elemental analysis was performed on Perkin–Elmer CHN PE 2400. Analytical TLCs were performed with silica gel 60 F_{254} plates. Visualization was accomplished by UV light or iodine vapour. Column chromatography was carried out using silica gel 60 (230–400 mesh ASTM). Melting points were determined without correction.

4.2. General procedure for the synthesis of 2-methyl-1,3,3a,9b-tetrahydrochromeno[3,4-*c*]pyrrol-4(2*H*)-ones (5a–e)

A stirred mixture of the corresponding coumarin **4** (1.0 mmol), paraformaldehyde (0.05 g, 1.7 mmol) and finely ground sarcosine (0.11 g, 1.2 mmol) was refluxed in dry benzene (8 mL) with removal of the water formed by means of a Dean–Stark trap. Reflux was continued for 4–7 h. The resulting mixture was cooled to room temperature and slowly filtered through a thin layer of silica gel, then washed with benzene. The colourless solution was evaporated in vacuo to give a crude product. Liquid adducts **5a**,**c** were converted to the oxalate form. Anhydrous oxalic acid (0.10 g, 1.1 mmol) dissolved in hot acetone (1.5 mL) was added with stirring to the crude product in hot acetone (1.5 mL). The mixture was refluxed for an additional 5 min with partial evaporation of acetone (to 2 mL).

After cooling to 5 °C, the solid that formed was filtered off and washed with dry acetone. The colourless powder was dried to a constant weight.

4.2.1. (3aS,9bS*)-2-Methyl-1,3,3a,9b-tetrahydrochromeno[3,4-c]pyrrol-4(2H)-one oxalate (**5a**).* Yield 78%, a colourless powder, mp 191–193 °C; IR: 2486, 1759, 1716, 1649, 1456, 1221, 1185, 1165, 763, 698 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.66 (s, 3H, MeN), 2.98 (t, J=10.0 Hz, 1H, H-1′), 3.45 (dd, J=10.8, 4.2 Hz, 1H, H-3′), 3.56 (t, J=9.0 Hz, 1H, H-1″), 3.64 (t, J=10.0 Hz, 1H, H-3″), 3.72 (td, J=8.8, 4.2 Hz, 1H, H-3a), 3.88 (q, J=9.0 Hz, 1H, H-9b), 7.03 (d, J=8.1 Hz, 1H, H-6), 7.14 (t, J=7.5 Hz, 1H, H-8), 7.30 (t, J=8.1 Hz, 1H, H-7), 7.32 (d, J=7.5 Hz, 1H, H-9); ^{13}C NMR (101 MHz, DMSO-d_6) δ 37.5 (C-9b), 40.0 (C-3a), 40.9 (MeN), 57.1 (C-3), 60.0 (C-1), 116.7 (C-6), 119.4 (C-9a), 124.8 (C-8), 129.1 (C-7), 129.3 (C-9), 150.1 (C-5a), 164.2 (CO_2H), 167.3 (C-4). Anal. Calcd for $C_{12}H_{13}NO_2\cdot(CO_2H)_2$: C, 57.34; H, 5.16; N, 4.78. Found: C, 57.06; H, 4.98; N, 4.81.

4.2.2. (3aS,9bR*)-2-Methyl-4-oxo-1,2,3,3a,4,9b-hexahydrochromeno[3,4-c]pyrrole-3a-carbonitrile (**5b**).* Yield 76%, a yellow viscous oil; ^1H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H, Me), 2.78 (dd, J=9.5, 6.4 Hz, 1H, H-1′), 3.23 (t, J=9.2 Hz, 1H, H-1″), 3.31 (d, J=9.8 Hz, 1H, H-3′), 3.57 (d, J=9.8 Hz, 1H, H-3″), 4.00 (dd, J=8.6, 6.4 Hz, 1H, H-9b), 7.10 (d, J=8.1 Hz, 1H, H-6), 7.18–7.23 (m, 2H, ArH), 7.31–7.36 (m, 1H, ArH); HRMS (ESI) calcd for $(C_{13}H_{12}N_2NaO_2)^+$ $[M+Na]^+$: 251.0791, found: 251.0799.

4.2.3. (3aS,9bR*)-Ethyl 2-methyl-4-oxo-1,2,3,3a,4,9b-hexahydrochromeno[3,4-c]pyrrole-3a-carboxylate oxalate (**5c**).* Yield 84%, a colourless powder, mp 164–166 °C; IR: 1766, 1744, 1659, 1252, 1165, 1144, 1099, 758, 691 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6+CD_3CO_2D) δ 1.10 (t, J=7.1 Hz, 3H, Me), 2.40 (s, 3H, MeN), 2.68 (dd, J=9.1, 8.4 Hz, 1H, H-1′), 3.22 (t, J=8.8 Hz, 1H, H-1″), 3.41 (AB-system, J=10.1 Hz, 2H, 3-CH_2), 3.90 (t, J=8.4 Hz, 1H, H-9b), 4.10 (q, J=7.1 Hz, 2H, OCH_2), 7.06 (d, J=8.2 Hz, 1H, H-6), 7.14 (td, J=7.5, 1.1 Hz, 1H, H-8), 7.27–7.33 (m, 2H, H-7, H-9); ^{13}C NMR (101 MHz, DMSO-d_6) δ 13.6 (Me), 41.0 (C-9b), 43.6 (MeN), 57.3 (C-3a), 61.3 (C-1), 61.7 (C-3), 62.6 (OCH_2), 116.6 (C-6), 119.4 (C-9a), 125.1 (C-8), 129.2 (C-7), 129.3 (C-9), 149.5 (C-5a), 162.8 (CO_2H), 164.9 (CO_2Et), 167.7 (C-4). Anal. Calcd for $C_{15}H_{17}NO_4\,(CO_2H)_2$: C, 55.89; H, 5.24; N, 3.83. Found: C, 55.94; H, 5.21; N, 3.76.

4.2.4. (3aS,9bR*)-N,N,2-Trimethyl-4-oxo-1,2,3,3a,4,9b-hexahydrochromeno[3,4-c]pyrrole-3a-carboxamide (**5d**).* Yield 87%, a colourless powder, mp 96–98 °C (diethyl ether); ^1H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H, Me), 2.56 (dd, J=9.0, 7.1 Hz, 1H, H-1′), 2.95 (s, 6H, 2Me), 3.15 (d, J=10.2 Hz, 1H, H-3′), 3.21 (dd, J=9.0, 7.3 Hz, 1H, H-1″), 3.80 (t, J=7.2 Hz, 1H, H-9b), 3.82 (d, J=10.2 Hz, 1H, H-3″), 7.06 (d, J=8.1 Hz, 1H, H-6), 7.15 (td, J=7.5, 1.0 Hz, 1H, H-8), 7.21 (dd, J=7.5, 1.6 Hz, 1H, H-9), 7.24–7.29 (m, 1H, H-7). Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.28; H, 6.69; N, 10.17.

4.2.5. Diethyl ((3aR,9bS*)-2-methyl-4-oxo-1,2,3,3a,4,9b-hexahydrochromeno[3,4-c]pyrrol-3a-yl)phosphonate (**5e**).* Yield 92%, colourless crystals, mp 126–128 °C; IR: 3017, 2905, 2844, 2789, 2766, 2755, 1755, 1492, 1456, 1391, 1339, 1148, 1014, 960, 759, 567 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, J=7.1 Hz, 3H, Me), 1.32 (t, J=7.1 Hz, 3H, Me), 2.38 (s, 3H, NMe), 2.75 (dd, J=9.3, 7.6 Hz, 1H, H-1′), 3.04 (t, J=9.2 Hz, 1H, H-1″), 3.21 (t, J=10.0 Hz, 1H, H-3′), 3.64 (dd, J=10.0, 4.2 Hz, 1H, H-3″), 3.72 (ddq, J=10.0, 8.6, 7.1 Hz, 1H, OC*H*H), 3.89 (dp, J=10.0, 7.0 Hz, 1H, OCH*H*), 4.05–4.15 (m, 1H, H-9b), 4.15 (dq, J=8.2, 7.1 Hz, 2H, OCH_2), 7.03 (dd, J=8.1, 1.1 Hz, 1H, H-6), 7.10 (td, J=7.5, 1.1 Hz, 1H, H-8), 7.19 (dd, J=7.5, 1.5 Hz, 1H, H-9), 7.25 (ddd, J=8.1, 7.5, 1.5 Hz, 1H, H-8); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.0 (d, J=5.8 Hz), 16.5 (d, J=6.1 Hz), 41.9, 42.3, 52.8 (d, J=140.1 Hz), 62.4, 63.1 (d, J=11.1 Hz), 63.5 (d, J=7.1 Hz), 63.9 (d, J=7.1 Hz), 116.8, 121.5, 124.8, 128.7, 128.9, 150.5, 166.4 (CO); ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.31 (s); HRMS (ESI) calcd for $(C_{16}H_{22}NNaO_5P)^+$ $[M+Na]^+$: 362.1128, found: 362.1149.

4.3. General procedure for the synthesis of tetrahydro-2*H*-spiro[chromeno[3,4-*c*]pyrrole-1,1′-cyclohexanes] 7

A stirred mixture of the corresponding coumarin **4** (1.0 mmol), cyclohexanone (0.10 g, 1.0 mmol), finely ground sarcosine (0.27 g, 3.0 mmol) was refluxed in dry toluene (3.3 mL) with removal of the water formed by means of a Dean–Stark trap. Reflux was continued for 48 h. The resulting mixture was cooled to room temperature followed by acidification with dilute HCl (5 equiv). The cycloaddition products **7c**,**e** were obtained from the aqueous layer by neutralization with $NaHCO_3$ and subsequent flash chromatography on silica gel using CH_2Cl_2:EtOAc as an eluent.

4.3.1. (3aS,9bR*)-Ethyl 2-methyl-4-oxo-3,3a,4,9b-tetrahydro-2H-spiro[chromeno[3,4-c]pyrrole-1,1′-cyclohexane]-3a-carboxylate (**7c**).* Yield 17%, a brownish powder, mp 87–91 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.66–0.77 (m, 1H), 1.04 (td, J=7.1, 0.9 Hz, 3H, Me), 1.01–1.07 (m, 1H), 1.12–1.21 (m, 1H), 1.21–1.29 (m, 1H), 1.40–1.52 (m, 2H), 1.52–1.62 (m, 3H), 1.77–1.87 (m, 1H), 2.49 (s, 3H, Me), 3.38 (s, 1H, H-9b), 3.55 (d, J=12.6 Hz, 1H, H-3), 3.93 (d, J=12.6 Hz, 1H, H-3′), 3.99–4.12 (m, 2H, OCH_2), 7.10 (d, J=8.2 Hz, 1H, H-6), 7.12–7.19 (m, 2H, H-8, H-9), 7.29 (t, J=7.5 Hz, 1H, H-7); ^{13}C NMR (101 MHz, $CDCl_3$) δ 13.9, 21.4, 22.7, 25.4, 29.1, 31.8, 38.3, 54.2, 58.1, 62.6, 63.0, 70.4, 117.0, 119.6, 124.4, 128.8, 129.7, 151.3, 168.0, 171.1; HRMS (ESI) calcd for $(C_{20}H_{26}NO_4)^+$ $[M+H]^+$: 344.1856, found: 344.1870.

4.3.2. Diethyl ((3aR,9bS*)-2-methyl-4-oxo-3,3a,4,9b-tetrahydro-2H-spiro[chromeno[3,4-c]pyrrole-1,1′-cyclohexan]-3a-yl)phosphonate (**7e**).* Yield 14%, a yellow powder, mp 127–132 °C; IR: 2977, 2929, 2860, 2799, 1749, 1689, 1594, 1443, 1260, 1247, 1212, 1035, 577 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.65–0.75 (m, 1H), 0.82 (td, J=7.1, 0.4 Hz, 3H, Me), 0.95–1.07 (m, 1H), 1.15–1.27 (m, 2H), 1.32 (td, J=7.1, 0.3 Hz, 3H, Me), 1.42–1.65 (m, 5H), 1.78–1.87 (m, 1H), 2.48 (s, 3H, Me), 3.51 (d, J=13.0 Hz, 1H, H-3), 3.56 (d, J=17.4 Hz, 1H, H-9b), 3.51–3.62 (m, 1H, OCH_2), 3.80 (dq, J=10.0, 7.0 Hz, 1H, OCH_2), 3.96 (dd, J=13.0, 9.9 Hz, 1H, H-3′), 4.15 (dq, J=8.2, 7.1 Hz, 2H, OCH_2), 7.06 (dd, J=8.1, 1.2 Hz, 1H, H-6), 7.13 (td, J=7.5, 1.2 Hz, 1H, H-8), 7.22 (dd, J=7.5, 1.7 Hz, 1H, H-9), 7.26–7.31 (m, 1H, H-7); ^{13}C NMR (101 MHz, $CDCl_3$) δ 15.9 (d, J=6.5 Hz), 16.5 (d, J=6.0 Hz), 21.2, 22.8, 25.5, 29.0, 31.4, 38.8, 51.3 (d, J=133.9 Hz), 61.5, 63.4 (d, J=7.9 Hz), 64.0 (d, J=7.7 Hz), 77.4, 116.6, 124.3, 128.6, 129.6, 151.7, 167.8; ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.09 (s); (ESI) calcd for $(C_{21}H_{31}NO_5P)^+$ $[M+H]^+$: 408.1934, found: 408.1938.

4.4. General procedure for the synthesis of pyrrolizidines 8–11 and indolizidines 12–15

A stirred mixture of the corresponding coumarin **4** (1.0 mmol), paraformaldehyde (0.05 g, 1.7 mmol) and finely ground proline (0.13 g, 1.1 mmol) or pipecolinic acid (0.14 g, 1.1 mmol) was refluxed in dry benzene (8 mL) with removal of the water formed by means of a Dean–Stark trap. After 4–8 h the resulting solution was evaporated in vacuo to give a crude mixture of products. They were isolated by column chromatography on silica gel using CH_2Cl_2:EtOAc as eluent. Alternatively, major diastereomers were purified by crystallization of the crude mixture of oxalates from acetone or ethanol–water.

4.4.1. (6aS,6bR*,11aR*)-Ethyl 6-oxo-6,6a,6b,7,8,9,11,11a-octahydrochromeno[3,4-a]pyrrolizine-6a-carboxylate (**8c**).* Yield 47%, a yellowish oil; IR (the oxalate): 2978, 2764, 2654, 1775, 1743, 1462,

1342, 1227, 1155, 1030, 1003, 764, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (free base) δ 1.19 (t, J=7.1 Hz, 3H, Me), 1.55 (dddd, J=11.9, 11.1, 9.1, 6.9 Hz, 1H, C*H*H), 1.81 (ddq, J=12.3, 11.0, 6.5 Hz, 1H, C*H*H), 1.89–1.96 (m, 1H, CH*H*), 1.96–2.04 (m, 1H, CH*H*), 2.65 (ddd, J=10.6, 9.0, 5.6 Hz, 1H, H-9′), 2.81 (t, J=12.3 Hz, 1H, H-11′), 3.13 (dd, J=12.5, 7.2 Hz, 1H, H-11″), 3.29 (ddd, J=9.0, 6.7, 1.7 Hz, 1H, H-9″), 3.82 (dd, J=12.1, 7.2 Hz, 1H, H-11a), 4.09 (dq, J=10.8, 7.1 Hz, 1H, OC*H*H), 4.18 (dq, J=10.8, 7.1 Hz, 1H, OCH*H*), 4.63 (dd, J=9.1, 7.0 Hz, 1H, H-6b), 7.05 (dd, J=8.5, 1.1 Hz, 1H, H-4), 7.12 (td, J=7.5, 1.1 Hz, 1H, H-2), 7.24–7.29 (m, 2H, H-1, H-3); ^1H NMR (400 MHz, DMSO-d_6) (the oxalate) δ 1.07 (t, J=7.1 Hz, 3H, Me), 1.60–1.80 (m, 2H, CH_2), 1.96–2.11 (m, 2H, CH_2), 2.91 (t, J=12.3 Hz, 1H, H-11′), 2.99 (td, J=10.6, 5.7 Hz, 1H, H-9′), 3.44 (dd, J=12.3, 7.4 Hz, 1H, H-11″), 3.43–3.48 (m, 1H, H-9″), 4.08 (dq, J=10.8, 7.1 Hz, 1H, OC*H*H), 4.14 (dq, J=10.8, 7.1 Hz, 1H, OCH*H*), 4.21 (dd, J=12.3, 7.4 Hz, 1H, H-11a), 4.67 (dd, J=9.4, 7.2 Hz, 1H, H-6b), 7.17 (d, J=8.2 Hz, 1H, H-4), 7.22 (td, J=7.5, 1.1 Hz, 1H, H-2), 7.37 (td, J=7.9, 1.6 Hz, 1H, H-3), 7.47 (dd, J=7.5, 1.6 Hz, 1H, H-1); ^{13}C NMR (101 MHz, DMSO-d_6) (the oxalate) δ 13.7, 25.5, 28.0, 40.0, 55.9, 60.3, 62.9, 69.6, 116.6, 118.8, 125.2, 129.5, 129.6, 150.0, 163.4 (CO), 163.6 (CO), 164.8 (CO). Anal. Calcd for $C_{17}H_{19}NO_4\cdot(CO_2H)_2$: C, 58.31; H, 5.41; N, 3.58. Found: C, 58.34; H, 5.40; N, 3.32.

4.4.2. (6aS,11aR*,11bR*)-Ethyl 6-oxo-6,6a,7,9,10,11,11a,11b-octahydrochromeno[4,3-a]pyrrolizine-6a-carboxylate (**9c**).* Yield 11%, a yellowish oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90–1.02 (m, 1H), 1.06 (t, J=7.1 Hz, 3H, Me), 1.37–1.47 (m, 1H), 1.56–1.69 (m, 1H), 1.70–1.78 (m, 1H), 2.70 (td, J=10.0, 6.0 Hz, 1H, H-9′), 3.23 (ddd, J=9.4, 7.0, 2.3 Hz, 1H, H-9″), 3.66 (d, J=12.4 Hz, 1H, H-7′), 4.01 (d, J=12.4 Hz, 1H, H-7″), 4.03 (d, J=9.7 Hz, 1H, H-11b), 3.95–4.04 (m, 1H, H-11a), 4.03–4.16 (m, 2H, OCH_2), 7.10 (dd, J=8.2, 1.1 Hz, 1H, H-4), 7.14 (td, J=7.4, 1.1 Hz, 1H, H-2), 7.19 (dd, J=7.6, 1.8 Hz, 1H, H-1), 7.29 (ddd, J=8.2, 7.2, 1.8 Hz, 1H, H-3); HRMS (ESI) calcd for $(C_{17}H_{20}NO_4)^+$ $[M+H]^+$: 302.1387, found: 302.1383.

4.4.3. (6aS,11aS*,11bR*)-Ethyl 6-oxo-6,6a,7,9,10,11,11a,11b-octahydrochromeno[4,3-a]pyrrolizine-6a-carboxylate (**10c**).* Yield 10%, a yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (t, J=7.1 Hz, 3H, Me), 1.82–2.04 (m, 4H, $2CH_2$), 2.73–2.80 (m, 1H, H-9′), 3.03–3.09 (m, 1H, H-9″), 3.25–3.29 (m, 2H, H-7), 3.35 (ddd, J=10.2, 6.7, 3.7 Hz, 1H, H-11a), 4.03 (dq, J=10.8, 7.1 Hz, 1H, OC*H*H), 4.08 (dq, J=10.8, 7.1 Hz, 1H, OCH*H*), 4.17 (d, J=10.2 Hz, 1H, H-11b), 7.11 (dt, J=7.6, 1.2 Hz, 1H, H-2), 7.11 (dd, J=8.2, 1.2 Hz, 1H, H-4), 7.17 (dd, J=7.6, 1.8 Hz, 1H, H-1), 7.30 (ddd, J=8.2, 7.3, 1.8 Hz, 1H, H-3); HRMS (ESI) calcd for $(C_{17}H_{20}NO_4)^+$ $[M+H]^+$: 302.1387, found: 302.1378.

4.4.4. (6aS,6bR*,11aR*)-N,N-Dimethyl-6-oxo-6,6a,6b,7,8,9,11,11a-octahydrochromeno[3,4-a]pyrrolizine-6a-carboxamide oxalate (**8d**).* Yield 60%, a pale yellow powder, mp 147–152 °C (ethanol). IR: 3017, 2529, 1755, 1712, 1646, 1177, 1150, 762, 712, 687 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6+CCl_4) δ 1.47–1.58 (m, 1H, H-7′), 1.81–1.93 (m, 1H, H-8′), 2.00–2.09 (m, 1H, H-7″), 2.13–2.21 (m, 1H, H-8″), 2.81 (s, 3H, MeN), 2.95 (t, J=13.0 Hz, 1H, H-11′), 3.09 (s, 3H, MeN), 3.09–3.15 (m, 1H, H-9′), 3.45 (dd, J=12.4, 7.0 Hz, 1H, H-11″), 3.63 (dd, J=9.7, 7.0 Hz, 1H, H-9″), 4.38 (dd, J=13.4, 7.0 Hz, 1H, H-11a), 4.94 (dd, J=10.4, 7.5 Hz, 1H, H-6b), 7.01 (d, J=8.2 Hz, 1H, H-4), 7.15 (t, J=7.5 Hz, 1H, H-2), 7.28 (td, J=7.8, 1.3 Hz, 1H, H-3), 7.43 (d, J=7.5 Hz, 1H, H-1); ^{13}C NMR (101 MHz, DMSO-d_6) δ 25.3 (C-8), 27.8 (C-7), 37.0 (MeN), 37.1 (MeN), 41.3 (C-11a), 54.1 (C-9), 55.8 (C-11), 60.4 (C-6a), 68.0 (C-6b), 116.1 (C-4), 119.7 (C-11b), 125.0 (C-2), 129.2 (C-3), 129.4 (C-1), 150.2 (C-4a), 161.1 (CO), 163.6 (CO_2H), 164.4 (C-6). Anal. Calcd for $C_{17}H_{20}N_2O_3\cdot(CO_2H)_2$: C, 58.46; H, 5.68; N, 7.18. Found: C, 58.50; H, 6.04; N, 6.87.

4.4.5. Diethyl ((6aR,6bR*,11aS*)-6-oxo-6,6a,6b,7,8,9,11,11a-octahydrochromeno[3,4-a]pyrrolizin-6a-yl)phosphonate oxalate (**8e**).* Yield 44%, white crystals, mp 133–136 °C (ethanol); IR: 2979, 2931, 2637, 1756, 1716, 1644, 1338, 1254, 1156, 1035, 1013, 772, 703 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.85 (t, J=7.1 Hz, 3H, Me), 1.21 (t, J=7.1 Hz, 3H, Me), 1.71–1.84 (m, 1H, C*H*H), 2.00–2.09 (m, 1H, CH*H*), 2.14–2.24 (m, 2H, CH_2), 2.93 (t, J=12.2 Hz, 1H, H-11′), 3.01 (td, J=11.1, 5.9 Hz, 1H, H-9′), 3.29 (tq, J=10.0, 7.0 Hz, 1H, OC*H*H), 3.45–3.53 (m, 2H, H-9″, H-11″), 3.70 (dquint, J=10.1, 7.1 Hz, 1H, OCH*H*), 3.97–4.12 (m, 2H, OCH_2), 4.17 (td, J=12.1, 7.6 Hz, 1H, H-11a), 4.63 (t, J=8.2 Hz, 1H, H-6b), 7.19 (dd, J=8.2, 1.0 Hz, 1H, H-4), 7.24 (td, J=7.5, 1.0 Hz, 1H, H-2), 7.42 (td, J=7.9, 1.5 Hz, 1H, H-3), 7.47 (dd, J=7.5, 1.5 Hz, 1H, H-1); ^{31}P NMR (162 MHz, DMSO-d_6) δ 17.62 (s); ^{31}P NMR (162 MHz, $CDCl_3$+CCl_4) (free base) δ 19.97 (s); HRMS (ESI, free base) calcd for $(C_{18}H_{25}NO_5P)^+$ $[M+H]^+$: 366.1465, found: 366.1462.

4.4.6. Diethyl ((6aR,11aR*,11bS*)-6-oxo-6,6a,7,9,10,11,11a,11b-octahydrochromeno[4,3-a]pyrrolizin-6a-yl)phosphonate (**9e**).* Yield 12%, amorphous paste; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (td, J=7.1, 0.5 Hz, 3H, Me), 1.33 (td, J=7.1, 0.5 Hz, 3H, Me), 0.93–1.02 (m, 1H, H-11′), 1.39–1.47 (m, 1H, H-11″), 1.56–1.67 (m, 1H, H-10′), 1.67–1.75 (m, 1H, H-10″), 2.66 (td, J=10.0, 5.9 Hz, 1H, H-9′), 3.21 (ddd, J=9.2, 6.7, 2.1 Hz, 1H, H-9″), 3.57 (ddq, J=10.0, 8.9, 7.1 Hz, 1H, OC*H*H), 3.63 (dd, J=12.4, 10.0 Hz, 1H, H-7′), 3.83 (dquint, J=10.0, 7.1 Hz, 1H, OCH*H*), 3.95 (td, J=9.4, 7.2 Hz, 1H, H-11a), 3.99 (dd, J=12.4, 1.1 Hz, 1H, H-7″), 4.08–4.17 (m, 2H, OCH_2), 4.10–4.18 (m, 1H, H-11b), 7.06 (dd, J=8.1, 1.2 Hz, 1H, H-4), 7.13 (td, J=7.5, 1.2 Hz, 1H, H-2), 7.23 (dd, J=7.6, 1.8 Hz, 1H, H-1), 7.28 (ddd, J=8.1, 7.5, 1.8 Hz, 1H, H-3); ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.96 (s); HRMS (ESI) calcd for $(C_{18}H_{24}NNaO_5P)^+$ $[M+Na]^+$: 388.1284, found: 388.1283.

4.4.7. (6aS,6bR*,11aR*)-6a-Benzoyl-6b,7,8,9,11,11a-hexahydrochromeno[3,4-a]pyrrolizin-6(6aH)-one oxalate (**8f**).* Yield 50%, pale yellow crystals, mp 144–147 °C (acetone); ^1H NMR (400 MHz, DMSO-d_6) δ 1.30–1.42 (m, 1H), 1.69–1.83 (m, 1H), 1.85–2.00 (m, 2H), 3.00–3.12 (m, 2H, NCH_2), 3.54 (dd, J=12.4, 7.2 Hz, 1H, NC*H*H), 3.52–3.60 (m, 1H, NCH*H*), 4.48 (dd, J=12.6, 6.9 Hz, 1H, H-11a), 5.33 (dd, J=9.5, 7.5 Hz, 1H, H-6b), 7.06 (d, J=8.0 Hz, 1H, H-4), 7.25 (t, J=7.4 Hz, 1H, H-2), 7.30–7.37 (m, 1H), 7.53–7.58 (m, 3H), 7.71 (d, J=7.4 Hz, 1H), 7.95 (d, J=7.8 Hz, 2H). Anal. Calcd for $C_{21}H_{19}NO_3\cdot(CO_2H)_2\cdot0.75H_2O$: C, 63.22; H, 5.19; N, 3.21. Found: C, 63.24; H, 4.96; N, 3.25.

4.4.8. (6aS,6bS*,11aR*)-6a-Methyl-6b,7,8,9,11,11a-hexahydrochromeno[3,4-a]pyrrolizin-6(6aH)-one hydrochloride (**11g**).* Yield 41%, a white powder, mp 187–192 °C; ^1H NMR (400 MHz, $CDCl_3$, the free base) δ 1.49 (s, 3H, Me), 1.68–1.81 (m, 2H, CH_2), 1.90–1.98 (m, 2H, CH_2), 2.41 (ddd, J=9.9, 8.4, 6.7 Hz, 1H, H-9′), 2.97 (dd, J=11.0, 7.1 Hz, 1H, H-11′), 3.01 (ddd, J=9.9, 6.9, 3.7 Hz, 1H, H-9″), 3.31 (t, J=6.9 Hz, 1H), 3.56–3.62 (m, 2H), 7.03 (d, J=8.3 Hz, 1H, H-4), 7.11 (td, J=7.6, 1.2 Hz, 1H, H-2), 7.22–7.28 (m, 2H, H-1, H-3). Anal. Calcd for $C_{15}H_{17}NO_2\cdot HCl$: C, 64.40; H, 6.49; N, 5.01. Found: C, 64.56; H, 4.74; N, 4.98.

4.4.9. Diethyl ((6aR,6bS*,12aS*)-6-oxo-6a,6b,7,8,9,10,12,12a-octahydro-6H-chromeno[3,4-a]indolizin-6a-yl)phosphonate (**12**) and diethyl ((6aR*,6bR*,12aS*)-6-oxo-6a,6b,7,8,9,10,12,12a-octahydro-6H-chromeno[3,4-a]indolizin-6a-yl)phosphonate (**13**).* Yield 51%, a white powder, mp 144–148 °C; IR: 2963, 2931, 2853, 1755, 1243, 1212, 1143, 1015, 795, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (**12**, 39%) δ 0.90 (t, J=7.1 Hz, 3H, Me), 1.29 (t, J=7.1 Hz, 3H, Me), 1.15–2.29 (m, 6H, $3CH_2$), 2.05–2.16 (m, 1H, H-10′), 2.17–2.27 (m, 1H, H-12′), 2.75 (ddd, J=20.7, 11.4, 2.4 Hz, 1H, H-6b), 3.08–3.15 (m, 1H, H-10″), 3.44 (t, J=8.0 Hz, 1H, H-12″), 3.69–4.24 (m, 5H, $2CH_2O$, H-12a), 7.02 (dd, J=8.1, 1.0 Hz, 1H, H-4), 7.09 (td, J=7.4, 1.0 Hz, 1H, H-2), 7.14–7.26 (m, 2H, H-1, H-3); ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.73 (s); ^1H NMR (400 MHz, $CDCl_3$) (**13**, 61%) δ 1.03 (t, J=7.1 Hz, 3H, Me), 1.33 (t, J=7.1 Hz, 3H, Me), 1.15–2.29 (m, 6H, $3CH_2$), 2.00 (td, J=11.7, 3.0 Hz, 1H, H-10′), 2.63 (td, J=10.9, 2.5 Hz, 1H, H-6b), 2.84 (t, J=9.2 Hz, 1H,

H-12′), 2.97–3.03 (m, 1H, H-10″), 3.04 (dd, *J*=9.0, 3.5 Hz, 1H, H-12″), 3.69–4.24 (m, 5H, $2CH_2O$, H-12a), 6.98 (dd, *J*=8.1, 1.0 Hz, 1H, H-4), 7.08 (td, *J*=7.5, 1.0 Hz, 1H, H-2), 7.14–7.26 (m, 2H, H-1, H-3); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.01 (s); HRMS (ESI) calcd for $(C_{19}H_{27}NO_5P)^+$ $[M+H]^+$: 380.1621, found: 380.1626.

4.4.10. Diethyl ((6aR,12aR*,12bS*)-6-oxo-6a,7,9,10,11,12,12a,12b-octahydro-6H-chromeno[4,3-a]indolizin-6a-yl)phosphonate (**14**).* Yield 12%, a colourless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, *J*=7.0 Hz, 3H, Me), 1.13–1.27 (m, 2H), 1.33 (td, *J*=7.0, 0.4 Hz, 3H, Me), 1.32–1.40 (m, 2H), 1.44–1.52 (m, 1H), 1.63–1.72 (m, 1H), 2.11 (td, *J*=11.6, 2.5 Hz, 1H, H-9′), 2.45 (t, *J*=10.5 Hz, 1H, H-12a), 2.78 (dd, *J*=8.0, 6.8 Hz, 1H, H-7′), 2.97–3.05 (m, 1H, H-9″), 3.71–3.83 (m, 1H, OC*H*H), 3.80 (d, *J*=8.4 Hz, 1H, H-7″), 3.83–3.93 (m, 1H, OCH*H*), 4.13 (dd, *J*=18.5, 10.0 Hz, 1H, H-12b), 4.17 (dq, *J*=8.2, 7.1 Hz, 2H, OCH_2), 6.99 (d, *J*=8.0 Hz, 1H, H-4), 7.06–7.11 (m, 2H, ArH), 7.20–7.25 (m, 1H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 15.9 (d, *J*=6.4 Hz), 16.5 (d, *J*=6.0 Hz), 24.3, 24.5, 28.1, 44.7, 51.8, 52.1 (d, *J*=140.5 Hz), 61.1, 63.2 (d, *J*=7.2 Hz), 63.4 (d, *J*=7.1 Hz), 67.1 (d, *J*=9.0 Hz), 116.5, 119.6, 124.2, 128.6, 129.9, 150.9, 166.5; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.14 (s); HRMS (ESI) calcd for $(C_{19}H_{27}NO_5P)^+$ $[M+H]^+$: 380.1621, found: 380.1640.

4.4.11. Diethyl ((6aR,12aS*,12bS*)-6-oxo-6a,7,9,10,11,12,12a,12b-octahydro-6H-chromeno[4,3-a]indolizin-6a-yl)phosphonate (**15**).* Yield 9%, an amorphous paste; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, *J*=7.1 Hz, 3H, Me), 1.00–1.14 (m, 1H), 1.29 (t, *J*=7.0 Hz, 3H, Me), 1.32–1.44 (m, 1H), 1.54–1.64 (m, 2H), 1.73–1.84 (m, 2H), 1.88 (t, *J*=10.5 Hz, 1H, H-12a), 2.00–2.10 (m, 1H, H-9′), 3.02–3.09 (m, 1H, H-9″), 3.19 (t, *J*=11.2 Hz, 1H, H-7′), 3.45 (dd, *J*=18.3, 10.3 Hz, 1H, H-12b), 3.68–3.80 (m, 1H, OC*H*H), 3.85–3.96 (m, 2H, OCH*H*, H-7″), 4.16 (dq, *J*=8.2, 7.1 Hz, 2H, OCH_2), 7.04 (dd, *J*=8.2, 1.0 Hz, 1H, H-4), 7.11 (td, *J*=7.5, 1.0 Hz, 1H, H-2), 7.19 (dd, *J*=7.5, 1.6 Hz, 1H, H-4), 7.24–7.30 (m, 1H, H-3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 15.9 (d, *J*=6.2 Hz), 16.5 (d, *J*=5.7 Hz), 23.4, 25.1, 28.7, 48.6, 49.7 (d, *J*=139.5 Hz), 52.2, 63.4 (d, *J*=7.0 Hz), 64.0 (d, *J*=7.1 Hz), 68.6 (d, *J*=11.9 Hz), 116.6, 119.3, 124.5, 128.9, 129.3, 150.5, 167.5; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.37 (s); HRMS (ESI) calcd for $(C_{19}H_{26}NNaO_5P)^+$ $[M+Na]^+$: 402.1441, found: 402.1447.

4.5. General procedure for the synthesis of 11-phenyloctahydrochromeno[3,4-*a*]pyrrolizines 16–17

A mixture of the corresponding coumarin **4** (1.0 mmol), benzaldehyde (0.04 g, 0.4 mmol) and finely ground proline (0.12 g, 1.0 mmol) was refluxed in dry toluene (8 mL) with magnetic stirring and removal of the water formed by means of a Dean–Stark trap. After 3 h, a second portion of benzaldehyde (0.04 g, 0.4 mmol) was added; after another 2 h, a third portion of benzaldehyde (0.04 g, 0.4 mmol) was added. Reflux was continued for an additional 4 h. Adducts **16** and **17** were isolated by column chromatography on silica gel using CH_2Cl_2:EtOAc as an eluent. Alternatively, for **17c**: the crude yellow reaction mixture was cooled to room temperature and slowly filtered through a thin layer of silica gel, then washed with toluene. Isopropanol (0.07 g, 1.2 mmol) and acetyl chloride (0.09 g, 1.1 mmol) were added with stirring to the solution, the resulting mixture was allowed to stand overnight at room temperature. The formed dark-magenta precipitate was dissolved in hot acetone, diluted with EtOAc and then kept for 2 days in a refrigerator. The colourless crystals of the product were filtered and washed with an acetone–ethyl acetate mixture. The hydrochloride of adduct **17c** was dried to a constant weight.

4.5.1. (6aS,6bS*,11R*,11aR*)-Ethyl 6-oxo-11-phenyl-6,6a,6b,7,8,9,11,11a-octahydrochromeno[3,4-a]pyrrolizine-6a-carboxylate (**16c**) and (6aS*,6bR*,11S*,11aR*)-ethyl 6-oxo-11-phenyl-6,6a,6b,7,8,9,11,11a-octahydrochromeno[3,4-a]pyrrolizine-6a-carboxylate (**17c**).* Yield 37%, a yellowish powder, mp 80–120 °C; ^1H NMR (400 MHz, $CDCl_3$) (**16c**, 36%) δ 1.04 (t, *J*=7.1 Hz, 3H, Me), 1.60–2.13 (m, 4H), 2.45–2.57 (m, 1H), 2.91–2.97 (m, 1H), 3.60 (d, *J*=10.6 Hz, 1H, CH), 3.73 (d, *J*=10.6 Hz, 1H, CH), 4.01–4.22 (m, 2H, OCH_2), 4.63 (t, *J*=7.4 Hz, 1H, H-6b), 6.37 (dd, *J*=7.5, 1.5 Hz, 1H, H-1), 6.62–7.47 (m, 8H, Ar); ^1H NMR (400 MHz, $CDCl_3$) (**17c**, 64%) δ 1.17 (t, *J*=7.1 Hz, 3H, Me), 1.60–1.71 (m, 1H), 1.85–2.13 (m, 3H), 2.87 (td, *J*=9.6, 6.0 Hz, 1H, H-9′), 3.35 (ddd, *J*=9.6, 6.9, 2.7 Hz, 1H, H-9″), 4.01–4.22 (m, 2H, OCH_2), 4.31 (d, *J*=8.7 Hz, 1H, CH), 4.39 (d, *J*=8.7 Hz, 1H, CH), 4.83 (dd, *J*=9.6, 6.8 Hz, 1H, H-6b), 6.82–7.36 (m, 9H, Ar); HRMS (ESI) calcd for $(C_{23}H_{24}NO_4)^+$ $[M+H]^+$: 378.1700, found: 378.1700.

4.5.2. (6aS,6bR*,11S*,11aR*)-Ethyl 6-oxo-11-phenyl-6,6a,6b,7,8,9,11,11a-octahydrochromeno[3,4-a]pyrrolizine-6a-carboxylate hydrochloride (**17c**).* Yield 0.49 g (26%), colourless crystals, mp 162–167 °C; IR: 2323, 1766, 1731, 1239, 1154, 756, 734, 699 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.16 (t, *J*=7.1 Hz, 3H, Me), 1.94 (br s, 1H), 2.19 (br s, 2H), 2.42 (br s, 1H), 3.60 (br s, 1H), 3.98 (br s, 1H), 4.15 (ABX_3-system, *J*=7.1, 10.8 Hz, 2H, OCH_2), 4.94 (br s, 1H), 5.42 (br s, 2H), 6.67 (dd, *J*=7.6, 1.6 Hz, 1H, H-1), 6.91 (d, *J*=7.6 Hz, 2H, Ph), 7.05 (t, *J*=7.5 Hz, 2H, Ph), 7.14 (t, *J*=7.4 Hz, 1H, Ph), 7.17–7.24 (m, 2H, H-2, H-4), 7.61 (d, *J*=7.0 Hz, 1H, H-4). Anal. Calcd for $C_{23}H_{23}NO_4 \cdot HCl$: C, 66.74; H, 5.84; N, 3.38. Found: C, 66.68; H, 6.00; N, 3.37.

4.5.3. Diethyl ((6aR,6bS*,11R*,11aS*)-6-oxo-11-phenyl-6,6a,6b,7,8,9,11,11a-octahydrochromeno[3,4-a]pyrrolizin-6a-yl)phosphonate (**16e**).* Yield 33%, an amorphous paste; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J*=7.1 Hz, 3H, Me), 1.32 (td, *J*=7.0, 0.4 Hz, 3H, Me), 1.82–2.00 (m, 2H), 2.02–2.14 (m, 1H), 2.48 (dt, *J*=10.2, 7.1 Hz, 1H), 2.74–2.83 (m, 1H), 2.83–2.93 (m, 1H), 3.49–3.59 (m, 1H, OC*H*H), 3.54 (dd, *J*=10.7, 1.7 Hz, 1H, H-11), 3.76–3.86 (m, 1H, OCH*H*), 3.90 (dd, *J*=14.4, 10.7 Hz, 1H, H-11a), 4.15 (dq, *J*=8.1, 7.1 Hz, 2H, OCH_2), 4.53 (dt, *J*=13.2, 7.0 Hz, 1H, H-6b), 6.40 (dd, *J*=7.5, 1.6 Hz, 1H, H-1), 6.87 (td, *J*=7.5, 1.1 Hz, 1H, H-2), 7.05 (dd, *J*=8.1, 1.1 Hz, 1H, H-4), 7.14–7.20 (m, 2H, Ph), 7.23 (ddd, *J*=8.1, 7.7, 1.6 Hz, 1H, H-3), 7.25–7.29 (m, 3H, Ph); ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.31 (s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.0 (d, *J*=5.8 Hz), 16.5 (d, *J*=6.3 Hz), 26.6, 27.8 (d, *J*=1.9 Hz), 53.0, 53.7 (d, *J*=138.0 Hz), 54.3, 63.5 (d, *J*=8.8 Hz), 63.9 (d, *J*=7.8 Hz), 71.0, 76.5 (d, *J*=14.6 Hz), 116.2, 120.0, 124.1, 128.0, 128.4, 128.9, 129.0, 150.8, 164.9; HRMS (ESI) calcd for $(C_{24}H_{29}NO_5P)^+$ $[M+H]^+$: 442.1778, found: 442.1777.

4.5.4. Diethyl ((6aR,6bR*,11S*,11aS*)-6-oxo-11-phenyl-6,6a,6b,7,8,9,11,11a-octahydrochromeno[3,4-a]pyrrolizin-6a-yl)phosphonate (**17e**).* Yield 21%, a yellow viscous oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.81 (t, *J*=7.1 Hz, 3H, Me), 1.34 (td, *J*=7.1, 0.3 Hz, 3H, Me), 1.82–2.30 (m, 4H, $2CH_2$), 2.81 (dt, *J*=10.4, 7.3 Hz, 1H, H-9′), 3.12–3.21 (m, 1H, H-9″), 3.15–3.26 (m, 1H, OC*H*H), 3.61–3.71 (m, 1H, OCH*H*), 4.13 (dq, *J*=8.3, 7.1 Hz, 2H, OCH_2), 4.29 (d, *J*=9.5 Hz, 1H, H-11), 4.37 (dd, *J*=16.1, 9.5 Hz, 1H, H-11a), 4.56 (ddd, *J*=10.2, 6.7, 1.6 Hz, 1H, H-6b), 6.64 (dd, *J*=8.1, 1.2 Hz, 1H, H-4), 6.89–6.94 (m, 2H, Ph), 6.96–7.01 (m, 3H, Ph), 7.06 (td, *J*=7.8, 1.7 Hz, 1H, H-3), 7.17 (dd, *J*=7.5, 1.7 Hz, 1H, H-1), 7.27–7.32 (m, 1H, H-2); ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.43 (s); HRMS (ESI) calcd for $(C_{24}H_{29}NO_5P)^+$ $[M+H]^+$: 442.1778, found: 442.1761.

4.6. Representative reactions of compounds 5

4.6.1. (3aR,9bS*)-3a-(Diethoxyphosphoryl)-2,2-dimethyl-4-oxo-1,2,3,3a,4,9b-hexahydrochromeno[3,4-c]pyrrol-2-ium iodide (**18**).* Methyl iodide (0.43 g, 3.0 mmol) was added to a stirred solution of the benzopyranopyrrolidine **5e** (0.34 g, 1.0 mmol) in anhydrous toluene (4 mL) at room temperature. The resulting mixture was stirred for 2 days at room temperature. The white precipitate was filtered, washed with anhydrous PhMe, Et_2O, and dried. Yield 0.43 g

(89%), a white powder, mp 187–192 °C (decomp.); IR: 2972, 1746, 1496, 1456, 1280, 1254, 1237, 1201, 1033, 1010, 779, 551 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.85 (t, J=7.0 Hz, 3H, Me), 1.24 (t, J=7.0 Hz, 3H, Me), 3.29 (s, 3H, NMe), 3.34 (s, 3H, NMe), 3.71–3.82 (m, 1H), 3.85–4.00 (m, 2H), 4.04–4.20 (m, 3H), 4.27–4.41 (m, 2H), 4.63 (ddd, J=19.0, 12.7, 6.9 Hz, 1H, H-9b), 7.22 (d, J=8.1 Hz, 1H, H-6), 7.27 (t, J=7.4 Hz, 1H, H-8), 7.45 (t, J=7.8 Hz, 1H, H-7), 7.57 (d, J=7.2 Hz, 1H, H-9); ^{13}C NMR (101 MHz, DMSO-d_6) δ 15.5 (d, J=6.0 Hz), 16.1 (d, J=5.7 Hz), 50.3 (d, J=136.6 Hz), 53.7, 54.3, 64.5 (d, J=7.1 Hz), 64.7 (d, J=7.2 Hz), 68.6 (d, J=11.6 Hz), 69.7, 115.7, 116.7, 125.2, 129.3, 130.1, 150.0, 163.5 (d, J=3.4 Hz); ^{31}P NMR (162 MHz, DMSO-d_6) δ 18.93 (s). Anal. Calcd for $C_{17}H_{25}INO_5P$: C, 42.43; H, 5.24; N, 2.91. Found: C, 42.41; H, 5.22; N, 2.92.

4.6.2. (3R,4S*)-Methyl 3-(diethoxyphosphoryl)-4-(2-hydroxyphenyl)-1-methylpyrrolidine-3-carboxylate (**19**).* A solution of the benzopyranopyrrolidine **5e** (0.34 g, 1.0 mmol) in methanol (4 mL) was refluxed for 10 min. The solvent was evaporated in vacuo to give an oily product. Yield 95%, a yellow viscous oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33–1.39 (m, 6H, 2Me), 2.51 (s, 3H, NMe), 2.83 (dd, J=9.5, 6.7 Hz, 1H, H-5′), 2.85 (dd, J=17.1, 10.2 Hz, 1H, H-2′), 3.14 (s, 3H, MeO), 3.17 (d, J=9.5 Hz, 1H, H-5″), 3.93 (dd, J=20.8, 6.7 Hz, 1H, H-4), 4.02 (dd, J=10.2, 6.0 Hz, 1H, H-2″), 4.16–4.24 (m, 4H, OCH_2), 6.66 (t, J=7.5 Hz, 1H, H-5(Ar)), 6.76 (d, J=8.0 Hz, 1H, H-3(Ar)), 6.94 (dd, J=7.6, 1.5 Hz, 1H, H-6(Ar)), 7.03–7.09 (m, 1H, H-4(Ar)); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.5 (d, J=6.2 Hz), 16.6 (d, J=5.8 Hz), 39.9, 50.7, 52.3, 59.0, 59.8 (d, J=142.0 Hz), 59.8 (d, J=2.9 Hz), 62.9 (d, J=7.4 Hz), 64.0 (d, J=6.9 Hz), 118.0, 118.1, 129.2, 132.6, 156.7, 168.8 (d, J=2.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.39 (s); HRMS (ESI) calcd for $(C_{17}H_{27}NO_6P)^+$ $[M+H]^+$: 372.1571, found: 372.1580.

4.6.3. (3aR,9bS*)-4-Ethoxy-3a-(hydroxymethyl)-2-methyl-1,2,3,3a,4,9b-hexahydrobenzo[5,6][1,2]oxaphosphinino[3,4-c]pyrrole 4-oxide (**20**).* Sodium borohydride (0.06 g, 1.7 mmol) was added to a stirred solution of the benzopyranopyrrolidine **5e** (0.34 g, 1.0 mmol) in ethanol (4 mL) and the resulting mixture was refluxed for 1 h. After cooling to room temperature, a solution of NH_4Cl (0.46 g, 8.5 mmol) in water (2 mL) was added. The solvents were evaporated in vacuo at 50 °C, then the residue was treated with warm ethanol (2×3 mL). An alcoholic solution was filtered and evaporated on a rotary evaporator. The crude product was dissolved in $CHCl_3$ (5 mL), and insoluble salts were filtered off. Evaporation in vacuo led to a white powder of alcohol **20**. Yield 0.29 g (96%), mp 87–91 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, J=7.0 Hz, 3H, Me), 2.65 (s, 3H, MeN), 2.85–2.93 (m, 1H, H-1′), 3.11 (dd, J=24.4, 12.0 Hz, 1H, H-3′), 3.94–4.06 (m, 3H, H-9b, OCH_2), 4.14 (dd, J=11.7, 2.5 Hz, 1H, OCH_2), 4.25 (dd, J=11.7, 3.6 Hz, 1H, OCH_2), 4.34 (t, J=13.1 Hz, 1H, H-3″), 4.73 (dd, J=11.0, 7.9 Hz, 1H, H-1″), 6.91 (d, J=8.0 Hz, 1H, H-6), 6.99 (t, J=7.0 Hz, 1H, H-8), 7.12 (d, J=7.4 Hz, 1H, H-9), 7.17 (t, J=7.7 Hz, 1H, H-7); ^{13}C NMR (101 MHz, $CDCl_3$) δ 17.3 (d, J=6.4 Hz), 39.5 (d, J=2.7 Hz), 44.7, 47.5 (d, J=135.0 Hz), 58.2, 61.0 (d, J=6.4 Hz), 63.6, 65.9 (d, J=5.2 Hz), 117.9, 122.6, 128.5, 129.3, 154.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 18.71 (s). HRMS (ESI) calcd for $(C_{14}H_{20}NNaO_4P)^+$ $[M+Na]^+$: 320.1022, found: 320.1035.

4.6.4. (3S,4R*)-3-Cyano-4-(2-hydroxyphenyl)-1-methylpyrrolidine-3-carboxylic acid (**21**).* Amino acid **21** was obtained by heating adduct **5b** (0.35 g, 1.5 mmol) in wet chloroform (5 mL) for 10 min at 50 °C. Yield 89% (0.33 g), an amorphous paste; ^1H NMR (400 MHz, $CDCl_3$) δ 2.52 (s, 3H, Me), 2.75 (dd, J=9.9, 7.8 Hz, 1H, H-5′), 3.16 (d, J=9.3 Hz, 1H, H-2′), 3.17–3.23 (m, 1H, H-5″), 3.61 (dd, J=7.8, 5.6 Hz, 1H, H-4), 3.64 (d, J=9.3 Hz, 1H, H-2″), 6.76 (td, J=7.4, 1.1 Hz, 1H, ArH), 6.87 (dd, J=8.1, 1.1 Hz, 1H, ArH), 7.02 (dd, J=7.4, 1.6 Hz, 1H, ArH), 7.17 (ddd, J=8.1, 7.4, 1.6 Hz, 1H, ArH), 10.6–12.1 (br s, 1H); HRMS (ESI) calcd for $(C_{13}H_{15}N_2O_3)^+$ $[M+H]^+$: 247.1077, found: 247.1082.

4.6.5. ((3S,4S*)-4-(2-Hydroxyphenyl)-1-methylpyrrolidin-3-yl)(piperidin-1-yl)methanone (**22**).* Piperidine (0.35 g, 4.1 mmol) was added to a stirred suspension of the oxalate **5a** (0.30 g, 1.0 mmol) in dry benzene (4 mL) and the resulting mixture was refluxed for 1 h. After cooling to room temperature, the precipitate of piperidinium oxalate was filtered off. Benzene was evaporated in vacuo. Yield 85%, a yellowish powder, mp 153–155 °C; IR: 3060, 2933, 2838, 2507, 1635, 1580, 1486, 1432, 1250, 1208, 753 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.94–1.03 (m, 1H), 1.12–1.24 (m, 2H), 1.25–1.35 (m, 2H), 1.36–1.46 (m, 1H), 2.36 (s, 3H, MeN), 2.61 (t, J=8.9 Hz, 1H, H-5′), 2.66 (dd, J=9.0, 5.5 Hz, 1H, H-2′), 2.77 (dd, J=9.0, 6.5 Hz, 1H, H-2″), 2.72–2.80 (m, 1H, NCH_2), 2.97–3.07 (m, 1H, NCH_2), 3.21 (ddd, J=12.6, 6.8, 3.5 Hz, 1H, NCH_2), 3.28 (dd, J=9.1, 5.5 Hz, 1H, H-5″), 3.41 (ddd, J=13.2, 6.6, 2.8 Hz, 1H, NCH_2), 3.64 (ddd, J=10.3, 8.9, 5.5 Hz, 1H, H-4), 3.91 (dt, J=10.3, 6.1 Hz, 1H, H-3), 6.58 (td, J=7.4, 1.2 Hz, 1H, H-5(Ar)), 6.62 (d, J=8.0 Hz, 1H, H-3(Ar)), 6.92–6.98 (m, 1H, H-4(Ar)), 6.96 (d, J=7.5 Hz, 1H, H-6(Ar)), 11.12 (br s, 1H, OH); ^{13}C NMR (101 MHz, DMSO-d_6) δ 24.0, 25.0, 25.5, 40.8, 41.7, 44.5, 45.6, 57.8, 61.7, 115.7, 117.4, 125.8, 127.4, 130.3, 156.0, 169.1. Anal. Calcd for $C_{17}H_{24}N_2O_2 \cdot 0.2H_2O$: C, 69.93; H, 8.42; N, 9.59. Found: C, 70.13; H, 8.67; N, 9.61.

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